

# Procter & Gamble

## PHARMACEUTICALS

Mail: The Procter & Gamble Company  
Health Care Research Center  
P.O. Box 8006  
Mason, Ohio 45040-8006

Shipping: The Procter & Gamble Company  
Health Care Research Center  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

November 28, 2000

Documents Management Branch  
Food and Drug Administration  
HFA-305  
5630 Fishers Lane.  
Rm. 1061  
Rockville, MD 20852

Re: Docket Number 0097D-1424

Dear Sir or Madam:

Procter & Gamble Pharmaceuticals has reviewed the Draft Guidance for Industry, Analytical Procedures and Methods Validation. We appreciate the opportunity to review this draft guidance and have the following comments.

### General Comments:

It is useful and appropriate for FDA to provide guidance on topics that are based on U.S. regulatory requirements, such as the "methods validation package". However, the draft guidance also covers many topics that are adequately covered by existing ICH guidelines, such as those on validation of analytical procedures, impurities, specifications and the common technical document. To have an additional FDA guideline that overlaps, expands, and sometimes contradicts the ICH guidelines is potentially confusing and contrary to the spirit of ICH.

An area where this guidance and ICH are in conflict is the reporting of impurities. In the draft guidance, there are several references to reporting impurities at the quantitation limit of the method, e.g., line 464. However, the ICH impurities guidelines establish the principle that impurities need not be reported below specified reporting limits. In many cases, the limits of quantitation of an analytical method is lower than the reporting limit specified in the ICH impurities guidelines, so requiring the reporting of impurities down to the quantitation limit of the method is beyond what is called for by ICH. We suggest FDA revise this guidance to reflect ICH standard and reference the ICH guideline.

In several places, the guidance recommends submission of raw data, calculations using raw data, and/or instrument output. There are instances when it is necessary to provide HPLC peak areas, absorbance values, or other instrument output, e.g., when demonstrating the linearity of an analytical method. However, the principles of calculating analytical results from instrument output are well established, explained in the method, and often performed automatically by the instrument or associated systems. Thus, reporting raw data or providing calculations using raw data is unnecessary and adds an additional regulatory burden that is not justified. If the intent is to check the data, calculations, or data systems the appropriate

2036 '00 NOV 29 A8:47

0097D-1424

C 16

time to do this is in an inspection. The focus of the CMC review should be to review the conclusions about the validation of the methods, which can be done without additional raw data or sample calculations.

The draft guidance attempts to provide direction in two general areas: 1) scientific practice and 2) submission requirements. However, in the current draft it is often difficult to distinguish between the two and it would be helpful to clearly separate them. Guidance on regulatory reporting could be usefully organized following the topics listed in the common technical document. Guidance on the areas of scientific practice could then be referenced, either in the appropriate ICH guidance, existing FDA documents, or appropriate sections of this new guidance.

**Specific Comments:**

| Line No.  | Comment  |
|-----------|--|
| 89-92     | <p>This paragraph expresses the principle that validated methods should be used for all aspects of product testing, however, it fails to recognize that different types and amounts of data are needed to validate a method. A more suitable wording might be:</p> <p>"Validated analytical procedures should be used for all aspects of product testing. The amount and type of data needed to validate a procedure depends on the type of method and its intended use. Guidance on the data needed can be found in the ICH methods validation guideline. In developing an analytical procedure care should be taken to ensure that the assay variation is appropriately small, considering the intended use of the procedure."</p> |
| 156       | <p>This suggests that a reference standard be of "highest purity." In reality, even compendial reference standards are not necessarily of the highest purity. The purity should be consistent with the intended use of the standard and the standard must be thoroughly characterized. This section should be revised to reflect this thought.</p>   |
| 195 - 206 | <p>This paragraph states that specific recommendations for validation of biological and immunochemical tests are not covered in this guidance document. Given that, we suggest this information on the characterization of reference standards for biological products be deleted as well.</p>   |
| 630-637   | <p>The first sentence of this section expresses the important thought that changes may introduce the need for revalidation. However, the second sentence, which starts "Revalidation should be performed to ensure ..." is a lengthy general statement on the purpose of validation. It obscures the next important thought that "The degree of revalidation depends on the nature of the change." We suggest deleting the second sentence in that paragraph.</p>  |
| 700       | <p>MSDSs should be provided by the sponsor for any materials provided to the FDA by the sponsor. However, it is impractical for the sponsor to pick and choose what other MSDSs should be provided to FDA. FDA should obtain the MSDS for any other material from the source of that material.</p>   |

*Procter&Gamble*

P&G Pharmaceuticals, Docket Number 99N-2100

| Line No. | Comment   |
|----------|---|
| 779      | In the second to the last sentence of this paragraph, the word "validated" is used to describe the process that the FDA lab uses to verify the appropriateness of the applicant's analytical procedure(s). This does not seem to be a correct use of "validate". The FDA lab does not "validate" methods, the applicant does. We would like to see this described as checked or verified. This also applies to lines 1079 and 1092.   |
| 845      | It should be specified that the RSD requirement is for repeated injections of standard solutions.   |
| 922      | "When manually operated equipment is used, the description of the analytical procedure should include an acceptance criterion for the amount of time that may elapse between sampling and reading". In our opinion, there is a need to evaluate this for both manual <i>and automated</i> methods. This a consideration in GC, HPLC, and other techniques, not just spectroscopic techniques. However, it should be specified as part of the system suitability in an application, only when this time period is critical to the procedure. |
| 1048     | The way in which the first sentence under <i>Procedure</i> is written gives the impression that the only suitable methods for dissolution testing are automated on-line analytical or manual sampling followed by HPLC analysis. In fact, these are only two examples of dissolution sample handling (for example, manual sampling followed by UV quantification may be feasible.) Putting "e.g." in the parenthetical statement would fix this.  |

If there are any questions or if I can be of further assistance, feel free to call on me. My phone number is 513-622-3914 and my email address is welles.hl@pg.com.

Sincerely,



Harry L. Welles, Ph.D.  
Principal Scientist  
Regulatory Affairs

MICHAEL D. SHILLEN  
PROCTOR & GAMBLE HCRC  
8700 MASON MONTGOMERY RD  
MASON OH 45040  
(513)622-1376

SHIP DATE: 28NOV00  
ACC # 175926763

ACTUAL WGT: 1 LBS SCALE

SEE ADDRESS LABEL ON PACKAGE FOR  
THIS SHIPMENT TO MD 20852

4635 2003 4330 **FedEx**

REF: HCS454

PRIORITY OVERNIGHT WED

cad # 0626125 28NOV00

TRK# 4635 2003 4330

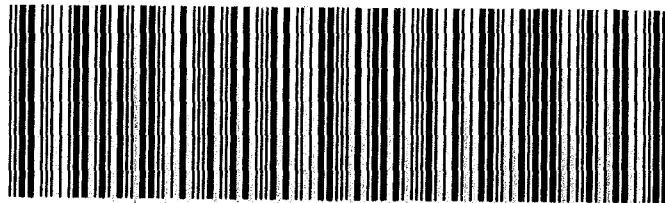
FORM  
0201

Deliver by:  
29NOV00

20852 -MD-US

IAD AA

NH GAIA



163078-077 RIT 0200

**From:**

**The Procter & Gamble Company**  
Sharon Woods Technical Center  
11450 Grooms Road  
Cincinnati, OH 45242

**TO:**

**Document Management Branch**  
**Food and Drug Administration**  
**HFA-305**  
**5630 Fishers Lane**  
**Room 1061**  
**Rockville, MD 20852**